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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,745	01/15/2004	Stefan M.C. Pype	2676-4555.1US	5708

24247 7590 01/03/2006

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,745	PYPE ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11 and 22-24* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☒ Claim(s) *22-24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 8-11 and 22-24 are pending.

The amendment filed 11/1/05 which cancels claims 1-7 and 12-21, and amends claims 9-11 has been entered. Please note that the objection(s) and/or rejection(s) not explicitly stated and/or restated below are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejection - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11 recite "*nucleotide similarity* ..."; the recitation is indefinite because the extent of similarity between two sequences can be based on percent sequence identity **and/or** conservation, and because the speciation does not define said recitation.

Claim Rejection - 35 USC 112, first paragraph

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the isolated polynucleotide that encodes the polypeptide comprising

amino acids 54-140 which is encoded by the polynucleotide of SEQ ID NO:1, does not reasonably provide enablement for a nucleotide sequence encoding a peptide fragment of the polypeptide thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2) The nature of the invention:

The current invention is directed to an isolated polynucleotide encoding polypeptide having activity of interacting with the tumor necrosis factor (TNT) receptor and a nucleotide sequence encoding the above-mentioned peptide fragment. The fragment encompasses a large number of *variants*, e.g., deletion mutants and truncation mutants derived from the SEQ ID NO:1 polynucleotide. The specification does not provide guidance and/or working examples in this regard. Screening and characterization of the any peptide fragment having ability of forming a complex *via* either direct interaction or indirect interaction with the members of TNF-receptor superfamily require a great deal of efforts and tests. The member of TNF-receptor superfamily is large (see the attachment "*TNF Receptor Superfamily*") and direct or indirect association between the said fragment and the member(s) vary depending on whether (i) the how

many protein factors involve in complex with the TNF receptor, e.g., three factors of the complex: {TNF-receptor (*genus*) •TNF associated factor (TRAF) [*genus*] •TRAF-interacting protein (I-TRAF)} (see Rothe et al. (1996) *Proc. Natl. Acad. Sci.* 93, 8241-8246); and (ii) state of oligomerization of said factor (e.g., TRAF proteins can form heterodimer or hetero-oligomer, see Mcwhirter et al. (1999) *Cold Spring Harb. Symp. Quant. Biol.* Vol. 64, pages 551-562), and thus, this would amplify complexity of the screening and test thereof, which would have required undue experimentation.

(3) The unpredictability of the art:

The variant polynucleotide (as small as that encoding 10 amino acid long peptide) would be expected to have unpredictable properties in comparison to the above-stated isolated polynucleotide encoding the polypeptide comprising amino acids 54-140, 54-362, 54-273, or 54-236 of the instant SEQ ID NO:2. It has been shown (Esparza et al. (2004) *CMLS, cell Mol. Life Sci.*, 61, 3087-3092) that mutations in TRAF type 4 (TRAF4) binding site of a TNF receptor result in elimination of the signaling capability of the TNF-receptor such as activating NF-κB (see page 3088, the left column of Esparza et al.), and loss of TRAF4-mediated regulation of NF-κB (see Figure 2). Because this signaling regulation requires formation a complex comprising TNF-receptor and TRAFs (see page 3087, the left column, the 1st paragraph), the mutations are unpredictable with regard to forming complex of the mutated TNF-receptor associated factor 4 (TRAF4) with the TNF-receptor. Also, Force et al. (*J. Biol. Chem.* (1997(272, 20835-30840) has taught that deletions of TRAF3 protein lead to defective interaction with lymphotoxin-β receptor (LβTR) which is *a member of TNF-receptor family* (see Figures 1-2 and pages 30839-30840), and that the deletions mutations are dominant negative inhibitors of a LβTR biological function (see

Figure 5), suggesting unpredictability of the deletion mutations, i.e., a truncated fragment of TRAF3 polypeptide.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to teach common attribute and characteristics that identify the variant/fragment peptide thereof. The specification needs to provide sufficient guidance to be considered enabling.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the variety of variant (deletion/truncation) molecules of the polynucleotide encoding the variant fragment thereof.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in mutagenesis, protein engineering as well as knowledge in immunology and skill in peptide chemistry. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

Sorting out domain(s) critical for the peptide fragment that comprises 10 or more than 10 amino acid residues of SEQ ID NO:2 to form a complex with a member of TNF-receptor (e.g., LβTR or CD40) requires a large quantity of efforts and tests including using a computer algorithm to predict structural parameters of the deletion mutations, as taught by Force et al. (see page 30839, the right column, the 2nd paragraph). An unduly level of skill is thus needed for one skilled in the art in order to make and characterize the variant fragments resulted from deletion/truncation mutagenesis of the SEQ ID NO:1 sequence.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Applicants' response to the rejection under 35 USC 112, first paragraph

The response filed 11/10/05 argues that the specification is enabling for the scope of the instant claims as paragraphs [0077]-[0080], Examples 3, 5 and 9 provide instruction for the methods of isolating protein that complexed with CD40 or isolating nucleic acid encoding the protein thereof, analyzing protein fragments for their association with TNF-receptor proteins, e.g., via yeast two-hybrid or co-immunoprecipitation assay (see page 7). The applicants' argument is found to be unpersuasive because the abovementioned the paragraphs and Examples does not provide sufficient guidance and/or teachings as to structural information of the protein fragments important for formation of the complex between the protein (encoded by the claimed polynucleotide) and TNF receptor but rather routine methodologies of investigating protein-protein interaction. In light of unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims (see the above rejection), it would take undue trials and errors to practice the claimed invention. One skilled in the art would be required to carry out

an undue experimentation for screening and characterizing the variety of variants or fragments (deletion/truncation) molecules of the polynucleotide encoding the variant fragment thereof. Thus, the specification is deemed to lack enablement under 35 USC § 112.

On page 7, the last paragraph, the response discusses the Esparza et al. reference with regard to the mutations in a TNF-receptor resulting in dramatic decrease of the signaling capability of the TNF-receptor, and argues that instant claim 8 does not recite the signaling capacity. The applicants' argument has been fully considered but not it is not persuasive because (i) the Esparza et al. reference teaches that the signaling is performed through interaction of TRAF4 with a TNF-receptor, *i.e.*, glucocorticoid induced TNF-receptor (GITR) (see page 3088, the left column, the 2nd paragraph), and (ii) in Figure 2 and page 3089, the reference shows that the mutations in the TNF-receptor leads to a defective interaction of TRAF4 with said mutated receptor, and thereby the decrease of said signaling capacity thereof. Note that the signaling capacity is a readout of the above-mentioned (protein-protein) interaction.

In addition, on page 8, the response argues that the undue experimentation is not required for the skilled artisan to screen for and characterize bioactive fragments comprising 10 or more amino acid residues of SEQ OD NO:2 protein as the skilled artisan may not be required to sort out the domains critical/important for forming the claimed protein complex. The applicants' argument is unpersuasive because as taught by Esparza et al. the TRAF-binding domain (site) is important/critical for interaction between TRAF4 and the TNF-receptor (GITR) (see page 3089, the left column, and Figure 2) established by the mutagenesis of the above-mentioned domain in GITR, wherein said interaction is necessary for formation the complex between TRAF4 and GITR thereof.

Claims 22-24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber, Jon, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
December 26, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER